

Presentation highlights: Tissue engineering

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BIOGRAPHICAL INFORMATION

Dr. Buddy D. Ratner, Professor of Bioengineering and Chemical Engineering at the University of Washington, received his PhD in Polymer Chemistry from the Polytechnic Institute of Brooklyn, New York. For over ten years, he directed the NIH-funded National Electron Spectroscopy for Chemical Analyses (ESCA) and Surface Analysis Center for Biomedical Problems (NESAC/BIO). In 1996, he assumed the directorship of University of Washington Engineered Biomaterials (UWEB), a National Science Foundation (NSF) Engineering Research Center.

He is editor of the *Journal of Undergraduate Research in BioEngineering*, former editor of the journal, *Plasmas and Polymers*, past president of the Society For Biomaterials, and author of over 300 scholarly works. Ratner is a fellow of the American Institute of Medical and Biological Engineering (AIMBE), The American Vacuum Society, and the Society For Biomaterials. In 2002, he was elected President of AIMBE and a member of the National Academy of Engineering.

Dr. Ratner's research interests include:

- biomaterials,
- polymers,
- biocompatibility,
- tissue engineering,
- surface analysis of organic materials,
- self-assembly, and
- RF-plasma thin-film deposition.

PRESENTATION

Two bioengineering projects are underway at the University of Washington that, along with other research, provide an overview of the state of the art in tissue engineering. The first is the Engineered Biomaterials program, or "UWEB," a National Science Foundation Engineering Research Center dedicated to advancing biomaterials. The second is the Bioengineered Autologous Tissues program, or "BEAT," which aims to develop a living piece of heart muscle.

Ideally, prosthetics must involve integration with the body at three levels: into the bone, for mechanical support; between natural and artificial skin; and between nerves and robotic components in the artificial limb. The study of biocompatible materials, while of great importance, points out the irony of this term: No synthetic material is truly accepted and integrated by the human body. The body attempts to rid itself of these materials; the classic "foreign body reaction" is one in which the body encapsulates foreign material in a thin collagenous sac. Several experiments with mice, in which implants made from a variety of synthetic "biomaterials"—platinum, silicon, polyurethane, rubber, even titanium—were introduced, all triggered the same reaction. If the body walls off all currently used biocompatible materials to isolate itself from an implant, it may be questioned how these materials can be called biocompatible.

Even corrosion-resistant titanium, often hailed as the king of biomaterials for its capability to integrate into the body, does not truly integrate. While the validity of "osseointegration" is acknowledged (See Presentation highlight "**Osseointegration**"), the longevity of titanium in the body can be characterized as only "fair." Theoretically, there is still an encapsulation process going on, albeit a smaller one, that mineralizes into the bone. Bone heals to within 100 or 200 Å of titanium, whereas other materials sit in a collagen bag, with spacing or a capsule substantially greater (e.g., 50 µm) than that, in the

classic foreign body reaction. Titanium is no different from other materials; it is just highly inert.

The implication of the foreign body reaction for state-of-the-art prosthetics technology is that structures, such as electrodes implanted under the skin, are encapsulated and gradually become less effective, their performance decreasing over time. The key to overcoming the foreign body reaction and developing truly biocompatible materials is finding “lock and key switches” that trigger the healing process. Essentially, these are clues to healing, the things that activate normal healing. The goal is to encourage specific interactions that stimulate healing and reconstruction, ultimately preventing the non-specific foreign body reaction.

Some of the many avenues of research under pursuit include:

1. “Stealth” materials—Materials are being designed that can enter the body and remain free of a layer of adsorbed protein, a phenomenon that appears to trigger the foreign body reaction. The goal is a Teflon-like substance that strongly resists the attachment of proteins. Materials with exceedingly low protein adsorption are candidates and can be made.
2. Porosity modulation—In an experiment in which two materials, having the same chemical makeup but different porosity, were implanted in mice for four weeks, the less porous material provoked a more vigorous foreign body reaction and was encapsulated in a dense, highly collagenous bag with few blood vessels running through it. The more porous material had a thinner sac with far greater vascularity. The implication is that porosity may be critical to biocompatibility.
3. Knockout proteins—When wounded, bioengineered “knock-out” mice lacking a specific protein, thrombospondin, showed ten times more vascularity at the healing site than mice having the protein. The effective elimination of critical endogenous factors (such as thrombospondin) from the wound site might promote improved healing.

Of equal interest and importance is the natural paradigm of healing presented by the Mexican Mole Salamander, known for its limb regenerating capability. Research that can lead to an understanding of how this animal can regenerate a limb so readily, while humans cannot, is of vital importance. Current efforts at tissue engineering—the concept of seeding cells into a porous matrix and promoting growth of an organ—are aimed at synthesizing a complicated tissue, such as heart muscle.

KEY POINTS

- Even titanium, perhaps the most biocompatible material known, provokes a slight encapsulation reaction from the body.
- The ideal biocompatible material for the treatment of limb loss will promote normal healing and avoid the foreign body reaction altogether.
- Paradigms exist in nature for limb regeneration. An important goal is to study these models and tease out technologies that can be applied to the human body.

REFERENCE INFORMATION

Citations

1. Ratner, BD. A perspective on titanium biocompatibility. In: *Titanium in medicine: Material science, surface science, engineering, biological responses and medical applications*. Berlin: Springer-Verlag; 2001.
2. Ratner, BD. Replacing and renewing: Synthetic materials, biomimetics, and tissue engineering in implant dentistry. *J Dent Educ* 2001;65:1341.
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Web Site

<http://www.uweb.engr.washington.edu/>.
[University of Washington Bioengineered Materials]